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Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study

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ABSTRACT

Background

Patients with HER2-positive early breast cancer (EBC) preferred subcutaneous (SC) trastuzumab, delivered via single-use injection device (SID), over the intravenous (IV) formulation (Cohort 1 of the PrefHer study: NCT01401166). Here we report patient preference, healthcare professional satisfaction, and safety data pooled from Cohort 1 and also Cohort 2, where SC trastuzumab was delivered via hand-held syringe.

Patients and Methods

Patients were randomized to receive 4 adjuvant cycles of 600 mg fixed-dose subcutaneous (SC) trastuzumab followed by 4 cycles of standard intravenous (IV) trastuzumab, or vice-versa. The primary endpoint was overall preference proportions for SC or IV, assessed by patient interviews in the evaluable ITT population.

Results

A total of 245 patients were randomized to receive SC followed by IV and 243 received IV followed by SC (evaluable ITT populations: 235 and 232 patients, respectively). SC was preferred by 415/467 (88.9%; 95% CI, 85.7–91.6; $P < .0001$; two-sided test against null hypothesis of 65% SC preference); 45/467 preferred IV (9.6%; 7–13); 7/467 indicated no preference (1.5%; 1–3). Clinician-reported adverse events occurred in 292/479 (61.0%) and 245/478 (51.3%) patients during the pooled SC and IV periods, respectively; 16 patients (3.3%) in each period experienced grade 3 events; none were grade 4/5.

Conclusion

PrefHer revealed compelling and consistent patient preferences for SC over IV trastuzumab, regardless of SID or hand-held syringe delivery. SC was well tolerated and safety was consistent with previous reports, including the HannaH study (NCT00950300). No new safety signals were identified compared to the known IV profile in EBC. PrefHer and HannaH confirm that SC trastuzumab is a validated and preferred option over IV for improving patients' care in HER2-positive breast cancer.

Word Count

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breast cancer; HER2/neu; patient preference; subcutaneous; trastuzumab

INTRODUCTION

Trastuzumab-containing regimens are standard of care for HER2-positive early breast cancer (EBC) and metastatic breast cancer (MBC) [1–3]. A 600 mg fixed-dose manual injection of subcutaneous trastuzumab (Herceptin® SC, F. Hoffmann-La Roche Ltd, Basel, Switzerland) given via hand-held syringe is approved by the European Medicines Agency for EBC and MBC as an alternative to conventional intravenous (IV) infusion, based on results of the phase III HannaH study (NCT00950300) [4, 5]. An SC single-use injection device (SID) has comparable pharmacokinetics and safety to the hand-held syringe [6].

Intuitively, SC trastuzumab should be more convenient for patients as administration requires only 2–5 minutes [7]. Objectively, reductions in patients' infusion chair time, healthcare professionals' time, and other hospital resources have been demonstrated [8, 9]. The international, open-label, randomized, PrefHer study (NCT01401166) examined patients' preferences in the adjuvant breast cancer setting for IV or SC delivery via two cohorts using both methods of SC trastuzumab administration (SID or hand-held syringe) [10]. We present additional and final results of patient preferences in the overall study population (data pooled from both cohorts).

METHODS

Patients

Patient eligibility criteria have been described previously [10] and are available in the supplementary material, available at *Annals of Oncology* online.

Study Design

After surgery and completion of (neo)adjuvant chemotherapy, patients were randomized to receive 4 adjuvant cycles of SC trastuzumab (600 mg fixed dose injected into the thigh over approximately 5 minutes) every 3 weeks followed by 4 cycles of IV (8 mg/kg loading dose if the patient was randomized to receive IV trastuzumab first, 6 mg/kg maintenance doses) every 3 weeks or vice-versa (the crossover period, which was assessed in this report) as part of their standard trastuzumab [10]. Stratification was by *de novo* and non-*de novo* trastuzumab groups. Patients received SC trastuzumab via the SID in Cohort 1 and the hand-held syringe in Cohort 2. Following the crossover period patients received IV trastuzumab in Cohort 1 (unless participating in SID self-administration) and SC trastuzumab via hand-held syringe in Cohort 2. The primary endpoint was the proportion of patients indicating an overall preference for SC or IV in each cohort, assessed by two study-specific telephone patient interviews (PINTs): one before randomization and one after the crossover period. PINTs were conducted by experienced telephone interviewers and were stringently quality-controlled to ensure impartial questioning. The first interview (PINT1) probed factors that could potentially influence preferences, such as previous experiences with drug delivery methods, needle phobias, and expected preferences for SC or IV

trastuzumab. The second interview (PINT2) probed patients' experiences with each administration method on-study, final preference, strength of the preference and reasons for it. Factors influencing preference, strength of the preference, and reasons for it were exploratory endpoints. Patients in the SID cohort with ≥2 cycles remaining after crossover had the option to self-administer the SID, with their satisfaction assessed by questionnaire after first and last self-administrations as an exploratory endpoint. Secondary endpoints were safety and tolerability (assessed using standard methods [11–13]), event-free survival, immunogenicity (anti-trastuzumab and anti-recombinant human hyaluronidase [rHuPH20] antibodies in blood samples, taken at baseline and pre-dose cycle 5, i.e. before crossover) in the SID cohort only, healthcare professional satisfaction (assessed by responses of gynecologists, oncologists, oncology/specialist chemotherapy nurses, other healthcare professionals to the questionnaire question "All things considered with which method of administration were you most satisfied?" after the crossover period), and healthcare professional-perceived time savings with SC trastuzumab, also assessed by questionnaire.

PrefHer was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participating patients provided written informed consent. Approval for the protocol was obtained from appropriate local and national independent ethics committees.

Statistical Analyses

Preference for SC was compared in a non-protocol-specified analysis with a two-sided test against a null hypothesis value of 65% [10]. Each cohort was

powered independently. Factors potentially influencing preference were assessed in terms of their effect on the primary endpoint using logistic regression (forward selection by stepwise regression with alpha 0.05) in an exploratory manner.

Statistical analyses were performed with SAS (version 9.1.3).

Adverse event (AE) analyses are descriptive only.

RESULTS

Patients

From October 27, 2011 to December 3, 2012, 488 patients were randomized (Figure 1). The safety population included 483 patients (five randomized patients did not receive study treatment): 243 SC→IV and 240 IV→SC. Twenty-four treated patients did not complete all 8 trastuzumab cycles during crossover owing to disease recurrence (nine patients), AEs (grade 2 congestive heart failure [one patient], left ventricular dysfunction [five patients: two grade 1, three grade 3], grade 2 arthralgia [one patient], grade 3 generalized erythema [one patient]), refusal of treatment (three patients), withdrawal of consent (two patients), loss to follow-up (one patient), and protocol violation (one patient in the hand-held syringe cohort with lung metastases was erroneously randomized and was withdrawn after receiving one trastuzumab cycle). Of these patients, eight received SC and IV and completed the primary endpoint question in PINT2; therefore, they were included in the evaluable ITT population. The remaining 16 patients did not complete the primary endpoint question; therefore, the evaluable ITT

population comprised 467 patients (235 patients SC→IV and 232 IV→SC). No data were missing as all evaluable ITT patients completed both PINTs. Baseline patient demographics, tumor characteristics, and treatment history were balanced between study arms (Table 1).

Patient Preference

Primary Endpoint

At PINT2, 88.9% of patients (415/467) preferred SC (95% CI, 85.7–91.6; $P < 0.0001$, two-sided test against the null hypothesis of 65% SC preference), 9.6% (45/467, 95% CI, 7.1–12.7) preferred IV, and 1.5% (7/467, 95% CI, 0.6–3.1) had no preference (Figure 2). Results were consistent in both study arms: SC→IV arm, 89.8% of patients (211/235, 95% CI, 85.2–93.3) preferred SC, 8.9% (21/235, 95% CI, 5.6–13.3) preferred IV, and 1.3% (3/235, 95% CI, 0.3–3.7) had no preference; IV→SC arm, 87.9% of patients (204/232, 83.0–91.8) preferred SC, 10.3% (24/232, 95% CI, 6.7–15.0) preferred IV, and 1.7% (4/232, 95% CI, 0.5–4.4) had no preference.

Exploratory Analysis: Strength of Preferences

Overall preference for SC was “very strong” in 64.9% of patients (303/467; 95% CI, 60.4–69.2), “fairly strong” in 17.3% (81/467, 95% CI, 14.0–21.1), and “not very strong” in 6.6% (31/467, 95% CI, 4.6–9.3). Overall preference for IV was “very strong” in 5.1% of patients (24/467, 95% CI, 3.3–7.6), “fairly strong” in 2.1% (10/467, 95% CI, 1.0–3.9), and “not very strong” in 2.4% (11/467, 95% CI, 1.2–4.2).

Exploratory Analysis: Reasons for Patients' Preferences

The two main reasons that patients gave for preferring SC were that it saved time and that it resulted in less pain/discomfort/side effects (Table 2). Patients reported that SC was the least painful method (60.6% [283/467 patients] vs 17.3% for IV [81/467]; 22.1% [103/467] reported no difference); it also caused less bother from bruising (41.1% [192/467] vs 16.1% [75/467]; 42.8% [200/467] reported no difference), or from irritation to the injection site (33.0% [154/467] vs 14.6% [68/467]; 52.5% [245/467] reported no difference).

Predefined Exploratory Endpoint: Factors Influencing Preference

There was a high preference by patients for SC trastuzumab regardless of whether they had received IV trastuzumab before enrollment (Figure 2). Four terms were found to be significant and therefore kept in the final stepwise logistic regression model to select factors that potentially influence preference (Supplementary Table S1): expected preferences given at PINT1 (odds ratio [OR] 2.98, 95% CI, 1.51–5.88), weight (OR 0.41, 95% CI, 0.17–0.97), needle phobia/anxiety (OR 0.31, 95% CI, 0.14–0.68), and IV delivery type for prior chemotherapy (OR 2.31, 95% CI, 1.21–4.41). However, these results should be interpreted with caution due to the low number of patients who expressed a preference for IV or expressed no preference.

Hypothetical preference from PINT1 was a factor that influenced final preferences. Of the patients who expressed a prior preference for SC, 94.0% (203/216) expressed a final preference for SC (Table 3). Of the patients who expressed a prior preference for IV or expressed no prior preference, 84.5% (212/251) expressed a final preference for SC.

Preference for SC was 91.5% (95% CI, 87.4–94.6) for patients receiving IV trastuzumab by cannula (236/258 patients), 85.8% (95% CI, 80.2–90.3) for those with a venous access device (175/204 patients), and 80.0% (95% CI, 28.4–99.5) for those who received IV trastuzumab by both venous access methods (4/5 patients). Patients also preferred SC over IV regardless of their country (Supplemental Table S2).

Exploratory Analysis: Hypothetical Preferred Location and Route of Trastuzumab Administration

Overall, 60.4% of patients (282/467, 95% CI, 55.8–64.9) expressed a hypothetical preference to receive SC at home (65.7% in the SID cohort [155/236, 95% CI, 59.2–71.7] and 55.0% in the hand-held syringe cohort [127/231, 95% CI, 48.3–61.5]) when asked during PINT2 (Supplemental Table S3).

Secondary Endpoint: Healthcare Professional Satisfaction

Two hundred thirty-five healthcare professional questionnaires were completed. Responses indicated that most respondents were more satisfied with SC administration (77.0% [181/235], 95% CI, 71.1–82.2) than with IV (3.0% [7/235], 95% CI, 1.2–6.0). The remaining 20.0% [47/235], 95% CI, 15.1–25.7) indicated no preference for either route.

Secondary Endpoint: AE Profile

The AE profile obtained during the crossover period at this interim safety analysis is shown in Table 4. Differences between rates in the pooled SC and

IV periods were driven by grade 1 events occurring more frequently during the SC period. Influenza, dermatitis, syncope, hypertension, left ventricular dysfunction, and dyspnea were the most common grade 3 AEs (0.4% of patients [two] each). No patients had a grade 4 or 5 AE. No serious AEs were considered to be related to trastuzumab and each was resolved without sequelae. Twenty-four of 483 patients experienced cardiac events, but only two instances were recorded as grade 3 (both were left ventricular dysfunction). No cardiac events were reported as serious and there was one case of congestive heart failure (grade 2; resolved without sequelae).

Secondary Endpoint: Immunogenicity

In the SC→IV and IV→SC arms, anti-trastuzumab antibody rates were 0% (0/114 evaluable patients [any patient with a pre-dose cycle 5 trastuzumab or rHuPH20 antibody result regardless of baseline result]) and 3.4% (4/119), respectively, and the anti-rHuPH20 antibody rates were 2.6% (3/115) and 7.6% (9/119), respectively. No association between AEs and the presence of anti-trastuzumab or -rHuPH20 antibodies was observed (data not shown).

DISCUSSION

Final preference results from PrefHer showed that patients strongly preferred SC trastuzumab, regardless of SID or hand-held syringe delivery. These data provide an impetus for a change in practice regarding trastuzumab administration, and patients should be offered the choice of route. Patients should be provided with timely, accurate and easily understandable information regarding the available routes of administration, and with the

evidence base accumulated showing the experiences and preference of patients who received both IV and SC. Future trial designs (including in MBC) might use the methodology employed in PrefHer, where appropriate, with patient preferences and the reasons for them assessed as an essential part of the protocol.

Patients consistently gave “time saving” as their main reason for SC preference [10, 14, 15], which was confirmed by quantitative data from a time-and-motion sub-study [8, 9]. The SID may save patients further time by potentially allowing self-administration at home: the location hypothetically preferred by almost two-thirds of the patients in the SID cohort.

SC trastuzumab was well tolerated and no new safety signals were identified compared to the known IV profile in EBC. Additional analyses of PrefHer have shown that the safety profile combined from both cohorts is not affected by switching from SC to IV or vice-versa [16], further supporting a change for patients who prefer this method. As with HannaH [17], trastuzumab and rHuPH20 anti-drug antibody rates were low and there was no correlation with safety; however, results should be interpreted with caution as anti-trastuzumab antibody rates may have been underestimated due to the presence of trastuzumab in the serum affecting detection of anti-trastuzumab antibodies in the assay.

Interpretation of safety analyses should also take into account the limitations of having a short period of time during which the events were recorded for this analysis (eight 3-weekly cycles). Future analyses will assess data from the continuation periods once all patients have completed follow-up.

The apparent discrepancy between increased clinician-reported AEs during the SC period and patients' reports of SC producing less pain, bruising, and irritation may have resulted from a more conservative approach to reporting due to inexperience with the SC formulation [4].

Healthcare professionals were more satisfied with SC regardless of administration method. The time-and-motion sub-study has shown that healthcare professional time and center costs may be substantially reduced using the SID or the hand-held syringe [8, 9], and that healthcare professional-perceived clinical management and efficiency was increased with either SC method, to the benefit of different stakeholders [9, 18]. Combined with the totality of the clinical and patient preference data, SC trastuzumab has been shown to provide benefits to both patients and healthcare systems.

In conclusion, PrefHer revealed compelling and consistent patient preference for SC trastuzumab, regardless of delivery method (SID or hand-held syringe). Healthcare professionals were also more satisfied with SC over IV administration and SC was well tolerated. Safety data, including immunogenicity, were consistent with previous reports and no new safety signals were identified compared to the known IV profile in EBC.

Based on data from HannaH and PrefHer, SC trastuzumab is the validated and preferred option over IV for improving patients' care in HER2-positive breast cancer.

KEY MESSAGE

PrefHer revealed compelling and consistent patient preference for subcutaneous (SC) trastuzumab, regardless of delivery by single-use injection device or hand-held syringe. SC trastuzumab was well tolerated and safety data, including immunogenicity data, were consistent with previous reports. No new safety signals were identified compared to the known intravenous trastuzumab profile in early breast cancer.

Character count

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DISCLOSURES

XP has held consultant/advisory roles for F. Hoffmann-La Roche Ltd, GlaxoSmithKline, and Teva, and has received honoraria from Sanofi-Aventis and Eisai. JG has held consultant/advisory roles for F. Hoffmann-La Roche Ltd, Teva, and Eisai, and has received honoraria from F. Hoffmann-La Roche Ltd, GlaxoSmithKline, and Novartis. VM has held consultant/advisory roles for Amgen, Celgene, and F. Hoffmann-La Roche Ltd, and has received honoraria from Amgen, Celgene, Pierre-Fabre, F. Hoffmann-La Roche Ltd, and Janssen-Cilag. AK has held consultant/advisory roles for, and received honoraria from, F. Hoffmann-La Roche Ltd. SV has held consultant/advisory roles for, and has received honoraria from, F. Hoffmann-La Roche Ltd, Novartis and Amgen, and has received research funding from F. Hoffmann-La Roche Ltd and Sanofi-Aventis. NS is an employee of, and holds stocks in,

F. Hoffmann-La Roche Ltd. SO is an employee of F. Hoffmann-La Roche Ltd. LF had held consultant/advisory roles for, and has received honoraria and research funding from, F. Hoffmann-La Roche Ltd. GC and VJ have no conflicts of interest to disclose.

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TABLES AND FIGURES

Table 1. Patient Demographics, Tumor Characteristics, and Treatment History (Evaluable Intention-to-Treat Population)

All patients received prior surgery. [a]There were 331 patients who were younger than 60 years and 136 who were 60 years or older. [b]Patients with T4 tumors received (neo)adjuvant chemotherapy and were eligible for the study. ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IV, intravenous; SC, subcutaneous; SD.

Table 2. Primary Reasons for Patients' Preferences (Evaluable Intention-to-Treat Population)

Responses to the question "What are the two main reasons for your preference?" were recorded verbatim by the interviewer. Four experienced researchers independently scrutinized the dataset and provided overarching themes or core categories for coding. When broad consensus about these had been reached, each researcher independently coded every patient's response; the researchers then reconciled codings with each other and determined if any thematic categories could reasonably be collapsed together or if a new category was required.

[a]Some patients gave only one reason or no reason. Percentages were calculated on a per-patient basis (*N* = 467).

[b]Statement based on patient preference and not reflective of clinical data.

IV, intravenous; SC, subcutaneous.

Table 3. Expected and Actual Preferences (Evaluable Intention-to-Treat Population)

CI, confidence interval; IV, intravenous; SC, subcutaneous.

Table 4. Adverse Event Profile During the Crossover Period (4 Cycles of SC Trastuzumab and 4 Cycles of IV Trastuzumab, Safety Population)

If a patient had multiple events of the same NCI-CTCAE grade or relationship category, they were counted only once in that NCI-CTCAE grade or relationship category.

Patients could be counted in both the SC and IV period columns.

[a]One patient had both grade 1 (mild) and grade 2 (moderate) diarrhea and so is counted once in each NCI-CTCAE grade and once overall.

[b]Three patients had both grade 1 (mild) and grade 2 (moderate) injection site reaction and so are counted once in each NCI-CTCAE grade and once overall.

ICH, International Conference on Harmonisation; IV, intravenous; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; SC, subcutaneous.

Figure 1. Trial Profile

[a]Patient was screened and randomized but was later found to have a left ventricular ejection fraction of 53%. No treatment was given on-trial.

[b]Patients who received at least one dose of study treatment.

[c]Patients who received at least one dose of SC trastuzumab and IV trastuzumab and completed PINT1 and the primary endpoint question in PINT2.

ITT, intention-to-treat; IV, intravenous; PINT, Patient Interview; SC, subcutaneous.

Figure 2. Patients' Preferences (Evaluable Intention-to-Treat Population)

Responses to the question "All things considered, which method of administration did you prefer?"

Error bars represent 95% confidence intervals.

IV, intravenous; SC, subcutaneous.

SUPPLEMENTARY DATA

Supplementary Table S1. Logistic Regression (Evaluable Intention-to-Treat Population)

Terms not kept in the final logistic regression were: study arm (SC→IV vs IV→SC), prestudy trastuzumab treatment, country, age (<60 vs 60 years), difficulty traveling to chemotherapy appointments (yes vs no), and IV delivery type for prior trastuzumab at PINT2.

CI, confidence interval; IV, intravenous; PINT, Patient interview; SC, subcutaneous.

Supplementary Table S2. Patient Preference by Country (Evaluable Intention-to-Treat Population)

CI, confidence interval; IV, intravenous; SC, subcutaneous.

Supplementary Table S3. Hypothetical Preferred Location and Route of Trastuzumab Administration (Evaluable Intention-to-Treat Population)

Responses to the question “So if you could choose IV or SC given at: cancer center or clinic, your local hospital, your GP or primary care physician’s office, or at your home by trained healthcare professionals which would you prefer?”

GP, general practitioner; IV, intravenous; SC, subcutaneous; SID, single-use injection device.

APPENDICES

Patient eligibility criteria

Sussex Health Outcomes Research & Education in Cancer (SHORE-C)

PrefHer study team

PrefHer study investigators

TABLES

Table 1. Patient Demographics, Tumor Characteristics, and Treatment History (Evaluable Intention-to-Treat Population)

	Arm A SC→IV *n* = 235	**Arm B IV→SC *n* = 232**
Age, years[a]		
Median	53.0	52.0
(min–max)	(29–78)	(27–76)
Weight, kg		
Median	68.0	66.0
(min–max)	(35.0–120.0)	(41.0–131.8)
ECOG at screening, n (%)		
0	194 (82.6)	187 (80.6)
1	41 (17.4)	44 (19.0)
Not done	0	1 (0.4)
TNM classification at diagnosis, n (%)		
Primary tumor[b]		
T0	2 (0.9)	5 (2.2)
T1	109 (46.4)	90 (38.8)
T2	97 (41.3)	100 (43.1)
T3	13 (5.5)	23 (9.9)
T4	9 (3.8)	14 (6.0)

Not assessable	4 (1.7)	0
Unknown	1 (0.4)	0
Lymph node status		
Negative	119 (50.6)	110 (47.4)
Positive	109 (46.4)	118 (50.9)
Not assessable	6 (2.6)	4 (1.7)
Unknown	1 (0.4)	0
HER2-positive, n (%)		
Yes	235 (100)	232 (100)
No	0	0
Trastuzumab prior to enrollment, n (%)		
De novo	47 (20.0)	47 (20.3)
Non-*de novo*	188 (80.0)	185 (79.7)
Previous treatment, n (%)		
Chemotherapy	234 (99.6)	232 (100)
Radiotherapy	145 (61.7)	141 (60.8)
Hormonal therapy	96 (40.9)	95 (40.9)
Lapatinib	0	2 (0.9)

All patients received prior surgery. [a]There were 331 patients who were younger than 60 years and 136 who were 60 years or older. [b]Patients with T4 tumors received (neo)adjuvant chemotherapy and were eligible for the study. ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IV, intravenous; SC, subcutaneous.

Table 2. Primary Reasons for Patients' Preferences (Evaluable Intention-to-Treat Population)

Reason category	Total, *n* (%)[a]	Example
SC preferred, *n* = 756 reasons given by 415 patients		
Time saving	375 (80.3)	*"It does affect me being there so many hours. With this it was 'Hello' and 'Bye' without having to spend hours with patients"*
Less pain/discomfort/side effects	160 (34.3)	*"The SC method was a lot less painful to me and my bruises faded faster than in the case of the intravenous method"*
Ease of administration	62 (13.3)	*"Nurses can take care of many patients at the same time"*
Convenience to patient	57 (12.2)	*"Busy mum with four young children – want to get on with life"*
Problems with IV	51 (10.9)	*"No veins to be found as my veins are collapsing"*
Less stress/anxiety	35 (7.5)	*"IV reminds one of chemo and*

		isn't very pleasant for the head"
Other	20 (4.3)	*"Safer – less risk of infections"*[b]
IV preferred, *n* = 64 reasons given by 45 patients		
Fewer reactions (less pain, bruising, irritation, etc.)	33 (7.1)	*"Irritation due to the SC"*
Other/don't know	10 (2.1)	*"Had to have the port flushed through when attending for SC sessions, so would have been easier just to use it anyway"*
Psychological	9 (1.9)	*"When you have IV, you arrive, settle yourself. You have about 30 minutes. You can discuss with the nurses and other patients. It's a feeling of being 'at home'."*
Perceived efficacy	6 (1.3)	*"I'm not quite convinced that SC has the same effect as IV"*[b]
Environment/staff	5 (1.1)	*"One has to go there anyway and one can sit there with other women and exchange experience"*
Ecological	1 (0.2)	*"Device is not environmentally*

considerations	*sustainable. It is all thrown away after use"*

Responses to the question "What are the two main reasons for your preference?" were recorded verbatim by the interviewer. Four experienced researchers independently scrutinized the dataset and provided overarching themes or core categories for coding. When broad consensus about these had been reached, each researcher independently coded every patient's response; the researchers then reconciled codings with each other and determined if any thematic categories could reasonably be collapsed together or if a new category was required.

[a]Some patients gave only one reason or no reason. Percentages were calculated on a per-patient basis (*N* = 467).

[b]Statement based on patient preference and not reflective of clinical data.

IV, intravenous; SC, subcutaneous.

Table 3. Expected and Actual Preferences (Evaluable Intention-to-Treat Population)

	PINT1: Preferred method of administration			
	IV	**SC**	**No preference**	**Overall**
	***n* = 46**	***n* = 216**	***n* = 205**	***N* = 467**
PINT2: Preferred method of administration, *n* (%)				
IV	11 (23.9)	12 (5.6)	22 (10.7)	45 (9.6%)
SC	33 (71.7)	203 (94.0)	179 (87.3)	415 (88.9%)
No preference	2 (4.3)	1 (0.5)	4 (2.0)	7 (1.5%)
SC preferred (exact binomial)				
Estimated proportion, %	71.7	94.0	87.3	88.9
95% CI	56.5 to 84.0	89.9 to 96.8	82.0 to 91.5	85.7 to 91.6

CI, confidence interval; IV, intravenous; PINT, Patient interview; SC, subcutaneous.

Table 4. Adverse Event Profile During the Crossover Period (4 Cycles of SC Trastuzumab and 4 Cycles of IV Trastuzumab, Safety Population)

	SC period (all arms pooled) *n* = 479	**IV period (all arms pooled) *n* = 478**
Adverse events (all NCI-CTCAE grades), *n* (%)	**292 (61.0)**	**245 (51.3)**
Grade 1 (mild)	253 (52.8)	195 (40.8)
Grade 2 (moderate)	116 (24.2)	106 (22.2)
Grade 3 (severe)	16 (3.3)	16 (3.3)
Grade 4 (life-threatening)	0	0
Grade 5 (death)	0	0
Most frequent adverse events (≥5% of patients in the SC, IV, or crossover periods, all NCI-CTCAE grades), *n* (%)		
Arthralgia	24 (5.0)	27 (5.6)

Grade 1 (mild)	20 (4.2)	22 (4.6)
Grade 2 (moderate)	4 (0.8)	5 (1.0)
Grade 3 (severe)	0	0
Asthenia	27 (5.6)	23 (4.8)
Grade 1 (mild)	15 (3.1)	18 (3.8)
Grade 2 (moderate)	12 (2.5)	5 (1.0)
Grade 3 (severe)	0	0
Hot flush	23 (4.8)	16 (3.3)
Grade 1 (mild)	16 (3.3)	10 (2.1)
Grade 2 (moderate)	7 (1.5)	6 (1.3)
Grade 3 (severe)	0	0
Fatigue	19 (4.0)	18 (3.8)
Grade 1 (mild)	13 (2.7)	12 (2.5)
Grade 2 (moderate)	6 (1.3)	6 (1.3)

Grade 3 (severe)	0	1 (0.2)
Nausea	25 (5.2)	14 (2.9)
Grade 1 (mild)	20 (4.2)	12 (2.5)
Grade 2 (moderate)	4 (0.8)	2 (0.4)
Grade 3 (severe)	0	0
Missing	1 (0.2)	0
Headache	20 (4.2)	16 (3.3)
Grade 1 (mild)	14 (2.9)	12 (2.5)
Grade 2 (moderate)	6 (1.3)	3 (0.6)
Grade 3 (severe)	0	1 (0.2)
Injection site pain	32 (6.7)	0
Grade 1 (mild)	28 (5.8)	0
Grade 2 (moderate)	4 (0.8)	0
Grade 3 (severe)	0	0

Injection site reaction	30 (6.3)[b]	0
Grade 1 (mild)	29 (6.1)	0
Grade 2 (moderate)	4 (0.8)	0
Grade 3 (severe)	0	0
Injection site erythema	27 (5.6)	0
Grade 1 (mild)	24 (5.0)	0
Grade 2 (moderate)	3 (0.6)	0
Grade 3 (severe)	0	0
Diarrhea	16 (3.3)[a]	12 (2.5)
Grade 1 (mild)	12 (2.5)	10 (2.1)
Grade 2 (moderate)	5 (1.0)	2 (0.4)
Grade 3 (severe)	0	0
Pain in extremity	18 (3.8)	7 (1.5)
Grade 1 (mild)	17 (3.5)	2 (0.4)

Grade 2 (moderate)	1 (0.2)	5 (1.0)
Grade 3 (severe)	0	0
Cardiac adverse events, *n* (%)	**11 (2.3)**	**14 (2.9)**
Ejection fraction decreased (grade 1 [mild])	4 (0.8)	2 (0.4)
Left ventricular dysfunction	2 (0.4)	6 (1.3)
Grade 1 (mild)	2 (0.4)	3 (0.6)
Grade 2 (moderate)	0	1 (0.2)
Grade 3 (severe)	0	2 (0.4)
Palpitations (grade 1 [mild])	3 (0.6)	2 (0.4)
Bradycardia	1 (0.2)	3 (0.6)
Grade 1 (mild)	1 (0.2)	2 (0.4)
Grade 2 (moderate)	0	1 (0.2)
Cardiac failure congestive (grade 2 [moderate], resolved without sequelae)	1 (0.2)	0

Extrasystoles (grade 1 [mild])	1 (0.2)	0
Angina pectoris (grade 2 [moderate])	0	1 (0.2)
Heart valve incompetence (grade 1 [mild])	0	1 (0.2)
Mitral valve incompetence (grade 1 [mild])	0	1 (0.2)
Electrocardiogram change (grade 1 [mild])	0	1 (0.2)
Serious adverse events (ICH E2A), *n* (%)	**4 (0.8)**	**4 (0.8)**
Breast expander infection	1 (0.2)	0
Axilla abscess	1 (0.2)	0
Benign breast adenoma	1 (0.2)	0
Hematoma (not at the injection site)	1 (0.2)	0
Wound infection	0	1 (0.2)
Influenza	0	1 (0.2)
Cholelithiasis	0	1 (0.2)
Suture-related complication (post-laparotomy)	0	1 (0.2)

Mental disorder	0	1 (0.2)
Related to study treatment	0	0
Fully resolved without sequelae	4 (0.8)	4 (0.8)
Study drug discontinued due to adverse events, *n* (%)	**5 (1.0)**	**6 (1.3)**

If a patient had multiple events of the same NCI-CTCAE grade or relationship category, they were counted only once in that NCI-CTCAE grade or relationship category.

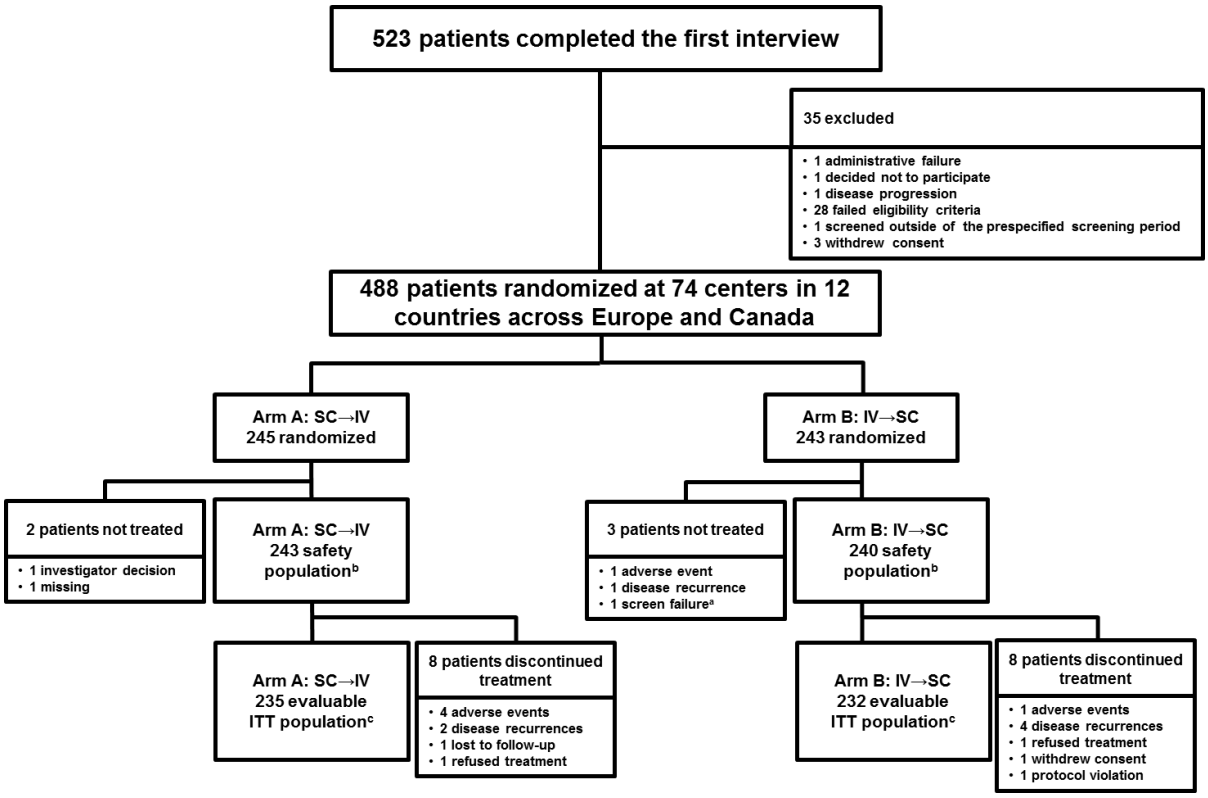
Patients could be counted in both the SC and IV period columns.

[a]One patient had both grade 1 (mild) and grade 2 (moderate) diarrhea and so is counted once in each NCI-CTCAE grade and once overall.

[b]Three patients had both grade 1 (mild) and grade 2 (moderate) injection site reaction and so are counted once in each NCI-CTCAE grade and once overall.

ICH, International Conference on Harmonisation; IV, intravenous; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; SC, subcutaneous.

Figure 1. Trial Profile



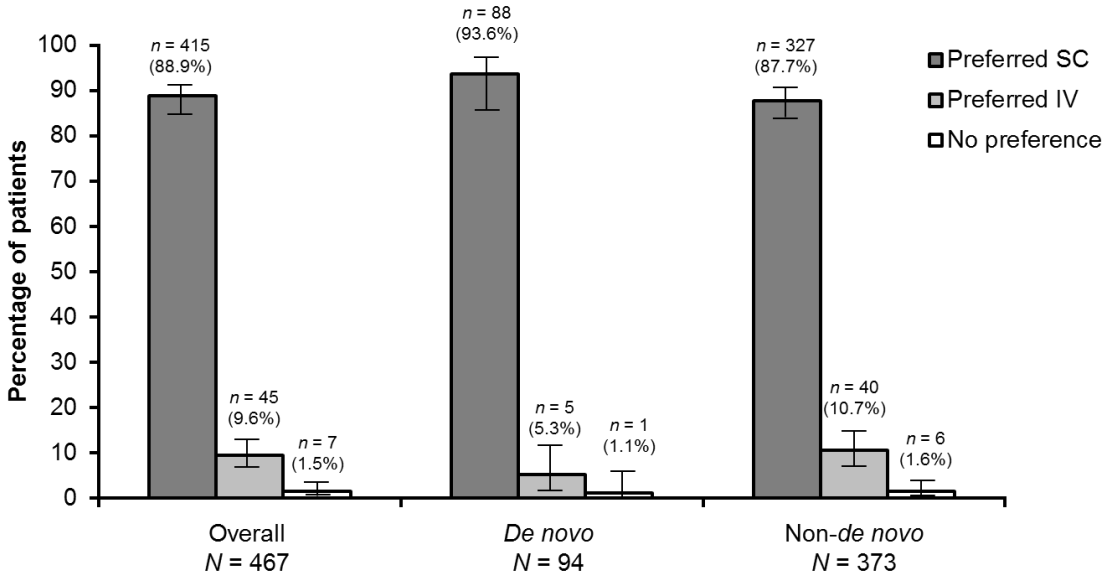
[a]Patient was screened and randomized but was later found to have a left ventricular ejection fraction of 53%. No treatment was given on-trial.

[b]Patients who received at least one dose of study treatment.

[c]Patients who received at least one dose of SC trastuzumab and IV trastuzumab and completed PINT1 and the primary endpoint question in PINT2.

ITT, intention-to-treat; IV, intravenous; PINT, Patient Interview; SC, subcutaneous.

Figure 2. Patients' Preferences (Evaluable Intention-to-Treat Population)



Responses to the question "All things considered, which method of administration did you prefer?"

Error bars represent 95% confidence intervals.

IV, intravenous; SC, subcutaneous.

SUPPLEMENTARY DATA

Supplementary Table S1. Logistic Regression (Evaluable Intention-to-Treat Population)

Factor	Preferred SC in PINT2, %	Odds ratio	95% CI
Expected preferences given at PINT1			
SC	94.0	2.98	1.51–5.88
IV/no preference	84.5		
Weight			
<80 kg	87.5	0.41	0.17–0.97
≥80 kg	92.9		
Needle phobia/anxiety			
Yes	77.6	0.31	0.14–0.68
No	90.2		
IV delivery type for prior chemotherapy at PINT1			
Cannula	93.3	2.31	1.21–4.41
Other *in situ* venous access devices	84.8		

Terms not kept in the final logistic regression were: study arm (SC→IV vs IV→SC), prestudy trastuzumab treatment, country, age (<60 vs 60 years), difficulty traveling to chemotherapy appointments (yes vs no), and IV delivery type for prior trastuzumab at PINT2.

CI, confidence interval; IV, intravenous; PINT, Patient interview; SC, subcutaneous.

Supplementary Table S2. Patient Preference by Country (Evaluable Intention-to-Treat Population)

Preference	Denmark *n* = 24	France *n* = 98	Germany *n* = 78	Italy *n* = 28	Russia *n* = 59	Spain *n* = 83	Sweden *n* = 10	Switzerland *n* = 8	Turkey *n* = 10	United Kingdom *n* = 35	Poland *n* = 17	Canada *n* = 17
Preferred method, *n* (%)												
IV	1 (4.2)	10 (10.2)	12 (15.4)	2 (7.1)	4 (6.8)	7 (8.4)	1 (10.0)	2 (25.0)	3 (30.0)	3 (8.6)	0	0
SC	23 (95.8)	85 (86.7)	65 (83.3)	26 (92.9)	55 (93.2)	76 (91.6)	9 (90.0)	6 (75.0)	5 (50.0)	32 (91.4)	17 (100)	16 (94.1)
No preference	0	3 (3.1)	1 (1.3)	0	0	0	0	0	2 (20.0)	0	0	1 (5.9)
SC preferred (exact binomial)												
Estimated proportion, %	95.8	86.7	83.3	92.9	93.2	91.6	90.0	75.0	50.0	91.4	100	94.1
95% CI	78.9–99.9	78.4–92.7	73.2–90.8	76.5–99.1	83.5–98.1	83.4–96.5	55.5–99.7	34.9–96.8	18.7–81.3	76.9–98.2	80.5–100	71.3–99.9

CI, confidence interval; IV, intravenous; SC, subcutaneous.

Supplementary Table S3. Hypothetical Preferred Location and Route of Trastuzumab Administration (Evaluable Intention-to-Treat Population)

Location and route	SID cohort overall, *n* (%) *N* = 236	Hand-held syringe cohort overall, *n* (%) *N* = 231	Combined overall, *n* (%) *N* = 467
IV at cancer center or clinic	7 (3.0)	14 (6.1)	21 (4.5)
SC at cancer center or clinic	44 (18.6)	50 (21.6)	94 (20.1)
IV at local hospital	2 (0.8)	2 (0.9)	4 (0.9)
SC at local hospital	8 (3.4)	7 (3.0)	15 (3.2)
IV at GP or primary care physician's office	2 (0.8)	2 (0.9)	4 (0.9)
SC at GP or primary care physician's office	12 (5.1)	21 (9.1)	33 (7.1)
IV at home	4 (1.7)	5 (2.2)	9 (1.9)
SC at home	155 (65.7)	127 (55.0)	282 (60.4)
Unknown	2 (0.8)	3 (1.3)	5 (1.1)

Responses to the question "So if you could choose IV or SC given at: cancer center or clinic, your local hospital, your GP or primary care physician's office, or at your home by trained healthcare professionals which would you prefer?"

GP, general practitioner; IV, intravenous; SC, subcutaneous; SID, single-use injection device.

APPENDICES

Patient eligibility criteria (Pivot X, Pivot X, Gligorov J, Müller V et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol 2013; 14: 962–970).

Eligible patients were women aged ≥18 years with HER2-positive (immunohistochemistry 3+ or *in situ* hybridization-positive), histologically confirmed primary invasive breast adenocarcinoma, no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant), an Eastern Cooperative Oncology Group performance status of 0 or 1, and a baseline left ventricular ejection fraction of ≥55% before the first trastuzumab dose. HER2-positivity was assessed by local laboratories with validated assays, according to recommendations outlined in the summary of product characteristics for IV trastuzumab. Radiotherapy or hormone therapy was allowed. Patients had to have been either trastuzumab-naïve (*de novo* group) or already receiving intravenous trastuzumab (non-*de novo* group) as part of their (neo)adjuvant therapy, and they had to have at least 8 out of the total 18 planned 3-weekly trastuzumab cycles remaining before enrollment.

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